Meta-analysis

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Statistics Collaborativ

Topics

- **Background**

- **Why we meta-analyze**

- **How to meta-analyze**

- **Choice of model**

- **Why the controversy**

Modern Background

G.V. Glass (1976). Primary, secondary and meta-analysis of research. Education Research 5:3-8.

Medical background

- **Popularized as "overviews" by Peto, Collins, Yusuf for cardiology in 80's**

Early background

When a number of quite independent tests of significance have been made,

it sometimes happens that

although few or none can be claimed individually as significant,

yet the aggregate give an impression that the probabilities are on the whole

lower than would often have been obtained by chance.

RA Fisher, 1925

Early examples

- 1904-K Pearson. Report on certain enteric fever inoculation statistics. BMJ 3, 3-10.

- 1931-J.L. Lush. Predicting gains in feeder cattle & pigs. J Agricultural Res 42, 853-881.

- 1933- RL Thorndike. The effect of the interval between test & retest on the constancy of the IQ. J Ed Psych 24 543-549.

Why we meta-analyze

- Does the therapy, *on average,* "work"?

    o What is a reasonable *estimate* of the magnitude of its effect?

- For what *subgroups* does the therapy work?

- Even if the therapy does not work on average, is there *a set of conditions* under which it is, or would be, effective?

- Is it worth doing *another study*?

How to meta-analyze

- stratified analysis

- studies as the strata
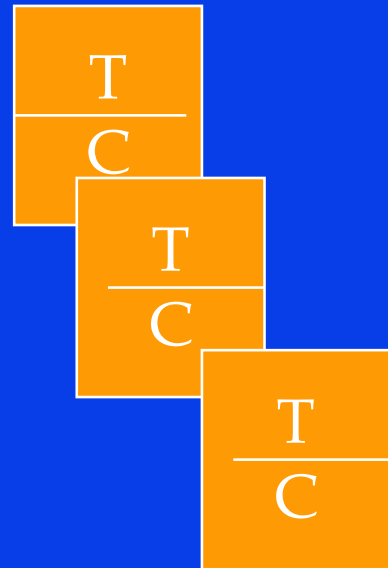
Questions

- What studies to include
- How to weigh individual trials
- Published and/or unpublished
- What endpoint
- What analytic techniques
- Pre or post hoc
- Published data vs. individual patient data

What studies to include

- **How similar should the treatments be?**

    o **Same intervention?**

    o **Same intensity?**

    o **For drugs, same dose?**

    o **For behavioral, how similar?**

    o **Same follow-up?**

Does dietary Cr affect fasting insulin?
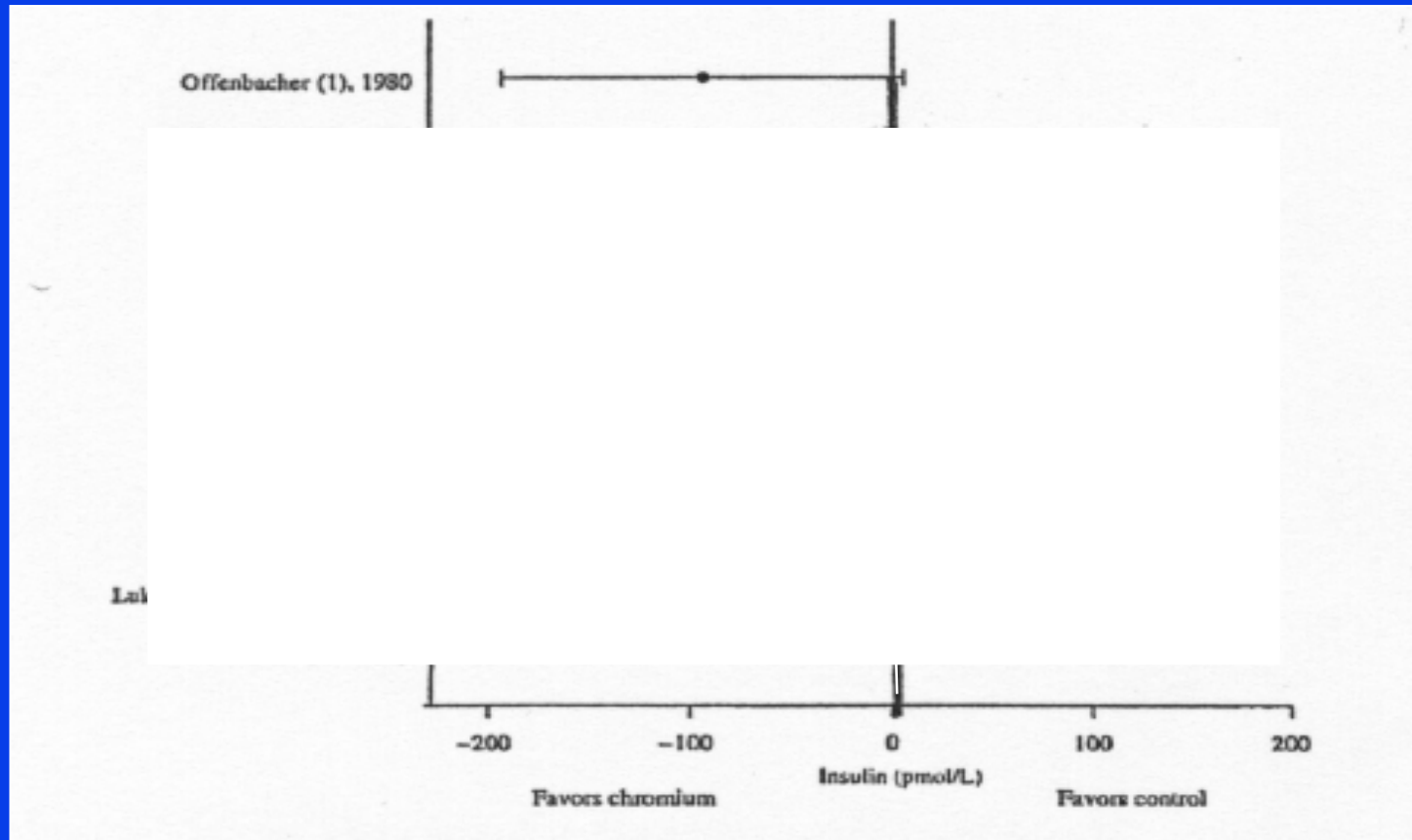
Dietary chromium supplements

- About 20 studies

- 1980 – 2000

- US, Israel, Finland, Netherlands, China, Canada

- Follow-up: 28 days to 16 mo

- Age: 18-23, 63-93, 42-83, ??, 30-74, etc.

- Blinding: single, not specified, double

Dose

- Brewer's yeast vs. Torula yeast

- $CrCl_3$ vs placebo

- $CrCl_3$+nicotinate+nicotinate

- "Cr-rich" yeast vs. placebo

- No two alike

Weighing individual trials

- Equal weight

- Weight by sample size

- Optimal weight

- By quality

Cr study

- **Smallest- 16:16**

  o US, non-diabetics, 200μg $CrCl_3$ + nicotinate vs. nicotinate; 28 day fu; age ≥65; blinding unspecified

- **Largest- 155:180**

  o China, diabetics, 1000 Cr-picrate vs. placebo; 4 mo fu; age 35-65; double-blind

- **Our method: by sample size**

Studies to include

- **Randomized vs. non-randomized?**

  - o **Meta-analysis can amplify bias**

- **Published vs. non-published**

  - o **File drawer study (uninteresting vs lousy)**

  - o **Not yet published**

Cr

- We found no file drawer papers

- We were given not-yet published data

What endpoint?

- More definitive the endpoint (e.g., mortality), the easier it is to include studies

- Want an endpoint that many studies include

- Want an endpoint likely to be measured similarly across studies

Cr example-endpoint

- **Mean fasting insulin at end of study**

- **Some studies**

  - **Mean fasting glucose**

  - **Mean glucose at 120 min**

  - **Mean fasting insulin**

  - **Mean insulin at 120 min**

Analytic techniques

- **Fixed vs. random effects conundrum**

  o **Fixed: assume you have the population of studies**

    o **Estimates the effect of those studies**

  o **Random: assume the studies come from a population of studies**

    o **Estimates the effect you would have in hypothetical studies**

The meta-analysis
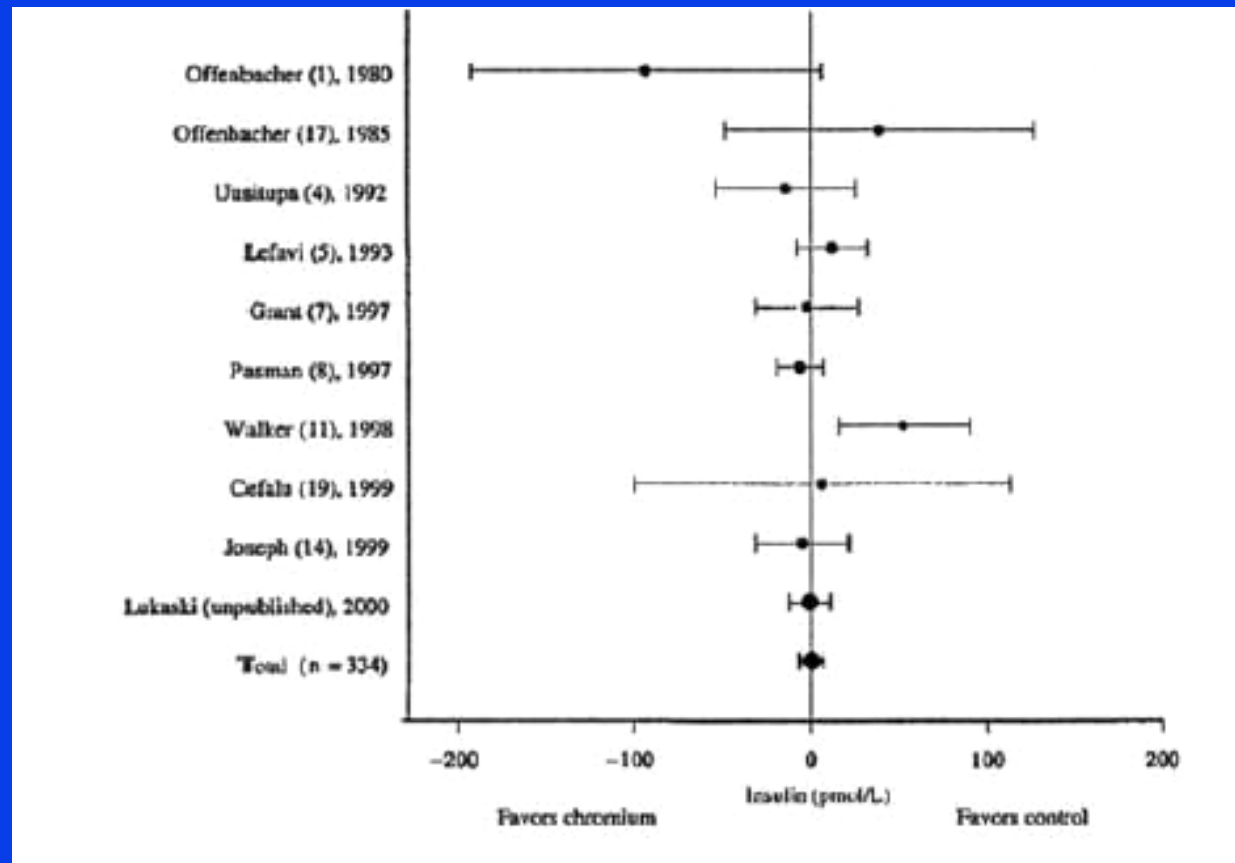
Follman and Proschan

- **Randomization test**

- **Emphasizes that you must have lots of studies for a meta-analysis to make sense**

Pre or post hoc

- Prespecified meta-analysis: gather the troops before you proceed

- Post-hoc, but with a protocol

- Post-hoc, no protocol

Individual patient vs. published data

- **Individual patient data is**

  - o   **More accurate**

  - o   **More flexible**

  - o   **More difficult**

  - o   **More expensive**

Steps

- **Decide why you are doing it**

- **Write a protocol with**

  o **Inclusion criteria**

  o **Methods**

- **Do an exhaustive search for papers**

- **Do analysis**

- **Do a "jackknife"**

- **Interpret carefully**